DIGITAL THERAPEUTICS ALLIANCE

DTx Value Assessment Dossier

DTx Product Evaluation: Clinical Evidence

Step 13: DTx Product Evaluation Types

Digital therapeutics undergo multiple evaluations throughout the product life cycle. These clinical and economic studies are used in the evaluation of product safety, effectiveness, real-world use, implementation, value assessment, and therapy optimization. In general:

» **Regulatory oversight:** Clinical pre-market evaluations are generally required to secure regulatory clearance and/or CE marking.

» **Coverage and reimbursement:** Clinical trials and economic evaluations are generally required for initial payor assessments.

» **Clinical practice:** Clinical trials and real-world data (RWD) are generally used to determine direct patient care and clinician decision making.

» **Clinical guidelines:** Clinical trials and real-world evidence (RWE) are generally used for DTx product incorporation into clinical guidelines.

The following overview provides the types of evaluations that a DTx product have undergone. Healthcare decision makers (HCDM) should conduct a thorough review of study design, outcomes, and quality of evidence.

Number completed	Number In progress	
		Observational Studies
_____	_____	*Descriptive:* Case report, case series, cross-sectional (descriptive or prevalence)
_____	_____	*Analytical:* Cross-sectional survey, case-control, cohort (prospective or historical)
_____	_____	*Implementation pilot:* Assess site-specific implementation capacity and value
_____	_____	*Localization pilot:* Assess cultural adaptation, language translation, linguistic accuracy/validation, etc.
_____	_____	Other:_____
		Experimental/Interventional Clinical Trials
_____	_____	Randomized Controlled Trial (RCT)
_____	_____	*Other controlled trials:* Non-randomized controlled trial, self-controlled study, crossover study
_____	_____	*Non-controlled studies:* Prospective single arm trial, open label trial, head-to-head comparative trial
_____	_____	Other:_____
		Real-World Outcomes
		RWD generation:
_____	_____	Product performance and technical outputs
_____	_____	End user and clinician engagement and satisfaction measures
_____	_____	Other:_____
		RWE generation:
_____	_____	Pragmatic clinical trial using an RCT-type design, with real-world elements
_____	_____	RWE as a retrospective or prospective observational study
_____	_____	Other:_____

Number completed	Number In progress	
		Product Analyses
_____	_____	*Retrospective analyses:* chart reviews, medical/pharmacy claims, electronic medical records, other novel data sources
_____	_____	*Expert reviews:* clinical practice guidelines, clinical pathways, Health Technology Assessment (HTA) agency evaluations, published systematic reviews
_____	_____	*Coverage decision assessments and formulary reviews:* external organization product evaluations, product indication reviews
_____	_____	*Patient perspectives:* insight into the practical use of therapies
_____	_____	Other:_____
		Economic Evaluation
_____	_____	Budget impact analysis
_____	_____	Cost-benefit analysis
_____	_____	Cost-effectiveness analysis
_____	_____	Cost-utility analysis
_____	_____	Cost-minimization analysis
_____	_____	Other:_____
		Systematic Review
_____	_____	Meta analysis
_____	_____	Other:_____

Step 14: Assessing Clinical Evidence Types

Digital therapeutics undergo clinical evaluations to assess product safety and clinical efficacy. Outcomes may also be used to determine therapy effectiveness, how the therapy should be used in target settings, length of therapy duration, the types of patients who may benefit, and appropriate use in clinical practice. Strong outcomes in studies often correlate to higher performing, lower risk products; reliable clinical outcomes and performance; and increased overall value of investment.

Check all that apply.

Study Basics

Study name:_____

Publication name and citation:_____

Trial registry number:_____

Was the study protocol modified after registering in clinicaltrials.gov or a similar registry? ☐ Yes ☐ No

If yes, describe how:_____

Study status:

- ☐ Study is currently underway
- ☐ Study is completed, but not published
- ☐ Study is completed and published
- ☐ Study forms the basis for regulatory clearance, CE marking, and/or product marketing claims
- ☐ Other:_____

Study partners (i.e., university, CRO):_____

Sponsor or funding source(s):_____

Has this study been peer-reviewed? ☐ Yes ☐ No ☐ Undergoing peer-review process

Study Design

Clinical study design used:

- ☐ Non-randomized controlled trial
- ☐ Prospective, single arm trial
- ☐ Cohort study
- ☐ Case-control study
- ☐ Case study
- ☐ RCT
- ☐ Pragmatic clinical trial
- ☐ RWE
- ☐ Other:_____

Study start and completion dates:_____

Study setting(s) and geographic location(s):_____

Trial design, randomization, and blinding procedures:_____

Study Population

Target population and subgroups:_____

Inclusion criteria:_____

Exclusion criteria:_____

Baseline patient characteristics and demographics:_____

Study population is representative of:

- ☐ General population
- ☐ Target population
- ☐ Other:_____

To mitigate bias, datasets are balanced across:

- ☐ Gender
- ☐ Ethnicity
- ☐ Age
- ☐ Other:_____

Clinical Outcomes

Key findings of the study:_____

Primary endpoint:_____

Secondary endpoints:_____

Comparator used:_____

Treatment and intervention used, dosing regimen:_____

Concomitant therapies, washout period:_____

Step 15: Assessing Quality of Clinical Evidence

Given the importance of clinical evidence in determining a DTx's clinical impact at the patient and population levels, HCDMs are encouraged to evaluate the quality of each study being submitted as part of the product's dossier.

Therefore, DTx manufacturers are asked to provide the following criteria based upon the tenets of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework per submitted clinical study.[1]

Check all that apply.

This study accounts for the following considerations:

Risk of Bias

- ☐ Potential limitations in the design or conduct of the study identified
- ☐ Conflicts of interest among study contributors identified
- ☐ Other:_____

Imprecision

- ☐ Study outcomes are inside of the 95% confidence interval
- ☐ The "n" is appropriate (i.e., a sample size that is powered appropriately for intended outcomes)
- ☐ Study analysis accounts for patient populations who have enrolled in the product, in addition to those who have been included in the study but declined participation
- ☐ Analytic methods address potential skewed, missing, or censored data; approaches to study adjustments; or population heterogeneity and uncertainty
- ☐ Other:_____

Inconsistency

- ☐ Multiple studies suggest similar clinical outcomes and have consistent confidence intervals
- ☐ Similarity between statistical and clinical significance relative to sample size
- ☐ Large magnitude of effect
- ☐ Other:_____

Indirectness

- ☐ Patients studied are similar to those for whom the clinical recommendation applies
- ☐ Interventions studied reflect actual practice
- ☐ Outcome studied is a surrogate for the appropriate outcome
- ☐ Other:_____

Publication Bias

- ☐ Potential holes in evidence are accounted for
- ☐ Outcomes are generated from experimental/interventional data
- ☐ Published studies underwent a peer-review process
- ☐ Other:_____

[1] https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/

Step 16: Types of Real-World Data (RWD) Generated by DTx Products

Through their ongoing use in patient care settings, DTx products generate a wide variety of RWD and outcomes that:

» Are made available to patients, caregivers, clinicians, and payors in line with patient privacy protections

» Form the foundation of decisions by clinicians and clinical teams

» Directly factor into RWE and economic analyses

With increasing frequency, DTx-generated outcomes and measures are replacing or supplementing outcomes generated through non-digital methods.

Check all that apply.

Digital therapeutics generate one or more types of RWD, outcomes, and insights depending on the product's purpose and functionality. Although this list is not comprehensive and will evolve, examples of RWD this product is able to produce include:

Clinical Measures

- ☐ Clinical outcomes (i.e., respiratory control, mobility, mental health status, FIM scores)
- ☐ State of medical condition (i.e., disease state severity, comorbidities)
- ☐ Digital endpoints (i.e., measures not previously available or assessed)
- ☐ Digital biomarkers (i.e., walking gait, joint mobility)
- ☐ Standardized patient assessments (i.e., GAD-7, PHQ-9, PSS)
- ☐ Patient-reported outcomes (PROs) (i.e., validated outcome measures, disease state triggers, pain perception)
- ☐ Physiologic data via associated sensors and hardware (i.e., pulse, breathing rates, blood pressure)
- ☐ Insight on related therapies (i.e., medication use and dosages, adherence patterns)
- ☐ Degree of disease state severity and change (i.e., condition improvement, deterioration)
- ☐ Other:_____

Product Functionality

- ☐ Product performance (i.e., product up/down time, functionality, internet connectivity)
- ☐ Analytics (i.e., system or product performance, efficiency)
- ☐ Quality measures (i.e., HEDIS, CAHPS measures)
- ☐ End user satisfaction measures (i.e., product acceptability, perceived helpfulness)
- ☐ Interoperability (i.e., EHR integration, performance related to connected or affiliated devices)
- ☐ Other:_____

Patient and Clinician Utilization

- ☐ User demographic data (i.e., age, gender, ethnicity)
- ☐ User geolocation (i.e., country, state, region)
- ☐ Utilization flow (i.e., gestural data, behavioral flow, performance data, utilization metrics)
- ☐ Patient engagement (i.e., time, frequency, duration of product utilization)
- ☐ Patient onboarding (i.e., consent documentation, patient/caregiver training, patient preferences)
- ☐ Patient utilization (i.e., registration, downloads, screen time usage, long-term retention)
- ☐ Patient adherence (i.e., completed vs. recommended modules, exercises, or lessons)

- ☐ Patient open-ended comments (i.e., patient preferences, satisfaction, surveys)
- ☐ Clinician inputs (i.e., prescribing parameters, authorization and discontinuation orders)
- ☐ Clinician engagement (i.e., registrations, initial and ongoing activity)
- ☐ Clinician implementation (i.e., utilization, frequency of use)
- ☐ Patient-clinician communications (i.e., scheduling, messaging)
- ☐ Patient, caregiver, clinician support service utilization (i.e., service type, frequency)
- ☐ Other:_____

Step 17: Utilizing DTx-Generated RWD

Compared to traditional medications, DTx products uniquely generate RWD, which includes a wide variety of data sets related to patient outcomes and product performance. RWD is generated on an ongoing basis by DTx products as a result of patient product use and is made available to patients and appropriate stakeholders in alignment with privacy and patient consent requirements.

Check all that apply.

How are DTx-generated RWD outcomes used in practice?

- ☐ Provide patients and caregivers with real-time insights on therapy progress and outcomes
- ☐ Generation of clinically actionable data to inform clinical decision making and optimize patient therapies
- ☐ Safety surveillance and adverse event identification
- ☐ Analysis of individual, subpopulation, and population trends and outcomes
- ☐ Payor-level de-identified data analysis for research purposes
- ☐ Short-term product functionality improvement and bug identification
- ☐ Long-term product improvement and iteration
- ☐ Other:_____

What additional data sources may be merged with DTx-generated RWD?

- ☐ Outputs from sensors, wearables, and other product plug-ins
- ☐ Validated patient assessment tools
- ☐ Electronic health record (EHR) and healthcare claims data
- ☐ Disease registry lists and outcomes
- ☐ Patient-generated insights
- ☐ Other:_____

Who is responsible for analyzing and delivering RWD outcomes?

- ☐ DTx manufacturer
- ☐ Health system
- ☐ Clinician
- ☐ HCDM/payor
- ☐ Other:_____

What level of the DTx-generated data source chain may reviewers and clinicians see?

- ☐ Raw data
- ☐ Processed data
- ☐ Data trends
- ☐ Other:_____

Commentary: RWD serves a vital role in the patient care continuum. Given the different purposes that RWD and RWE serve, when RWD is available, it may not be necessary to conduct a formal RWE study for direct patient care purposes. DTx-generated RWD is reliable and provides immediate and ongoing patient-specific insights.

Step 18: Development and Impact of Real-World Evidence (RWE)

Compared to RWD that is generated by DTx products on an ongoing basis and used by patients and clinicians in real time, RWE is developed through a formal clinical trial design process. RWE involves the formal analysis of RWD and other data sources to answer a specific clinical question related to the DTx product or related therapies, often conducted in the form of a prospective or retrospective observational study.

Check all that apply.

Conducting an RWE Study

What situations are most appropriate to develop RWE for this product?

- ☐ Inform a population-level decision
- ☐ Assess long-term DTx product clinical impacts
- ☐ Demonstrate that treatment effects are reproduced in broader populations or new clinical use settings
- ☐ Provide insights beyond those gathered in RCTs and RWD
- ☐ Assess DTx product use in a health system workflow
- ☐ Conduct a formal economic impact analysis
- ☐ Demonstrate impact on costs by using RWD in clinical practice
- ☐ Undertake a contractual requirements analysis (i.e., outcomes or value-based contracting)
- ☐ Other:_____

When may it not be necessary to conduct an RWE study?

- ☐ RCT and other studies have already demonstrated sufficient safety, efficacy, effectiveness, and economic outcomes for formulary placement and coverage decisions
- ☐ DTx-generated RWD data and analysis provide sufficient outcomes and metrics for clinicians and HCDMs
- ☐ System data analyses provide sufficient insights for clinical and economic assessments
- ☐ Other:_____

Benefit of RWE Studies

Which target groups are most likely to benefit from an RWE study for this product?

- ☐ Regulatory (i.e., post-market surveillance, product claims expansion)
- ☐ Clinicians (i.e., point-of-care decisions, determining how DTx use impacts other therapies and clinical outcomes, assessing short- and long-term health impacts)
- ☐ Patients (i.e., decisions related to healthcare options)
- ☐ HCDMs and payors (i.e., economic reviews, formulary review assessment, product use case evaluations, general research, risk reduction dashboards, quality improvement projects, population impact evaluations, background for future contractual considerations)
- ☐ Clinical guideline developers (i.e., clinical practice guideline decisions)
- ☐ Policy makers (i.e., product impact on populations, disease state improvements)
- ☐ Industry stakeholders (i.e., life sciences organizations)
- ☐ Other:_____

Evaluating an RWE Study

If the DTx manufacturer submits an RWE study as part of this Guide, the following criteria may be used to assess the trial.

Study name:_____

Study citation:_____

Who was responsible for conducting this RWE study?

- ☐ DTx manufacturer
- ☐ Health system or clinical team
- ☐ Employer
- ☐ Payor
- ☐ Academic institution
- ☐ Third-party entity
- ☐ Other:_____

What inputs were included in this RWE study?

- ☐ DTx-generated RWD outcomes
- ☐ Outputs from other devices, sensors, wearables, and plug-ins
- ☐ Health system sources (i.e., data from claims databases, EHRs, disease state registries)
- ☐ Other:_____

What considerations were incorporated in the RWE study design?

- ☐ Demonstrates that it is fit-for-purpose and of appropriate rigor
- ☐ Involves key stakeholders in designing and/or informing RWE studies
- ☐ Has pre-specified objectives, including specific hypotheses and target populations
- ☐ Ensures that data are collected and analyzed per pre-established protocols
- ☐ Provides opportunities to replicate study and outcomes
- ☐ Represents the real-world patient population
- ☐ Evaluates statistical significance and clinical meaningfulness in a representative sample of patients with the condition being treated
- ☐ Other:_____

RWE study outcomes are:

- ☐ Meaningful, providing relevant and context-informed evidence sufficient for interpretation, drawing conclusions, and making decisions
- ☐ Valid, meeting scientific and technical quality standards to allow causal interpretations
- ☐ Expedited, with incremental evidence synchronized with the decision making process
- ☐ Transparent, auditable, and reproducible
- ☐ Impactful, providing outcomes related to disease-specific healthcare resource utilization, evaluation of total healthcare resource utilization, etc.
- ☐ Other:_____

Where is/will the RWE study results be published?

- ☐ Publicly, in a peer-reviewed publication
- ☐ Publicly, available in a white paper
- ☐ Internal analysis (i.e., informal report, formal report)
- ☐ Other:_____

Who has/will have access to RWE study results?

- ☐ HCDM and/or payor
- ☐ HTA or formulary review committee
- ☐ Point-of-care clinician
- ☐ Patient and/or caregiver
- ☐ Publicly available
- ☐ Other:_____

Digital Therapeutics Alliance

Founded in 2017, the Digital Therapeutics Alliance (DTA) is a non-profit trade association of industry leaders and stakeholders engaged in the evidence-driven advancement of digital therapeutics. As the leading international organization on digital therapeutic thought leadership and education, DTA provides patients, clinicians, payors, and policy makers with the necessary tools to evaluate and utilize DTx products.

DTA's members—including organizations dedicated to manufacturing, evaluating, supporting, and utilizing DTx products—work to transform global healthcare by advancing high-quality, clinically validated digital therapeutics to improve clinical and health economic outcomes.